I. A SYNTHESIS OF PYRIDINES INVOLVING THE ALDOL CONDENSATION

II. THE PREPARATION OF 2-AMINOALKYL PYRIDINES

III. SYNTHETIC METHODS FOR 2-(2-PYRIDYL)-CYCLOPENTANONE

BY

RICHARD WILLIAM MEIKLE

B.S., Illinois Wesleyan University, 1943
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AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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PART ONE

A SYNTHESIS OF PYRIDINES INVOLVING THE ALDOL CONDENSATION

Introduction

The purpose of this investigation has been the development of a synthetic method for certain substituted pyridines employing a modification of the Chichibabin synthesis. The most recent investigations of the Chichibabin synthesis have been carried out by Frank and coworkers[1] who studied the scope of the synthesis as a practical method for obtaining substituted pyridines and determining the relation of the carbonyl starting compound to the yield and structure of the resulting pyridine derivatives.

Discussion Of The Results

It was postulated that substituted cyclohexenones, which can give rise to 1,5-dicarbonyl compounds by reverse aldol condensation, might be converted to pyridines under the conditions of the Chichibabin synthesis. The reaction is best carried out by heating the cyclohexenone in the temperature range 250-300° for a period of three hours using ten molar equivalents of ammonia and one molar equivalent of ammonium acteate in a steel, high-pressure autoclave. The 1,5-dicarbonyl compound is converted to the pyridine derivative by addition of ammonia and loss of water and hydrogen.

In any one reaction there is only one pyridine formed and it is stable under the conditions used.

The following pyridines were prepared in the course of the investigation: *sym*-collidine, 2-methyl-6-phenyl-, 2,6-dimethyl-4-phenyl-, and 2-ethyl-4-isopropenyl pyridines.

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PART TWO

THE PREPARATION OF 2-AMINOALKYL PYRIDINES

Introduction

In a search for compounds whose analgesic activity is somewhere between that of aspirin and that of types which cause addiction, other investigators have prepared aralkylamines with the amino group on the fourth or fifth carbon atom from the benzene ring. Several of these amines exhibited marked analgesic activity.[1]

2-Pyridyl isopropyl amines have also been prepared in recent studies, and have been tested for analgesic properties.[2] It was of interest, therefore, to develop methods of synthesis for two new 2-aminoalkyl pyridines carrying the amino group on the third carbon atom from the pyridine nucleus.

Discussion Of The Results

Various methods for the syntheses of two new 2-aminoalkyl pyridines, 1-(2-pyridyl)-3-aminobutane (I) and 1-(2-pyridyl)-3-aminopentane (II), have been investigated.

The prefered method of synthesis for these compounds is given below.

The amines I and II were synthesized by means of the Leuckart reaction employing 1-(2-pyridyl)-3-butanone and 1-(2-pyridyl)-3-pentanone, respectively. These ketones were obtained by the treatment of β-(2-pyridyl)-propionitrile with methyl- and ethyllithium, respectively.

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PART THREE

SYNTHETIC METHODS FOR 2-(2-PYRIDYL)-CYCLOPENTANONE

Introduction

The purpose of this investigation has been the development of a synthetic method for 2-(2-pyridyl)-cyclopentanone. This compound will serve as the precursor for α,α'- and α,β'-dipyridyls by employing the following reactions: formation and separation of isomeric oximes, conversion of the oximes to the corresponding α-piperidones via the Beckmann rearrangement, and conversion of these piperidones to the corresponding dipyridyls by application of a reaction described by Wallach[1] using phosphorus pentoxide and high temperatures.

Discussion Of Results

Various methods for the synthesis of 2-(2-pyridyl)cyclopentanone have been investigated.

The first method of synthesis involved the condensation of 2-bromopyridine and 2-carbethoxycyclopentanone with subsequent hydrolysis and decarboxylation of the product to give the desired compound. The condensing agents used were dimethylaniline, powdered potassium, sodium hydride, and sodium ethoxide but in no case was the reaction successful.

Another approach to the synthesis of 2-(2-pyridyl)-cyclopentanone consisted of converting 1-(2-pyridyl)-cyclopentanol, prepared from pyridine, cyclopentanone, and aluminum according to the procedure of Lochte, Thomas and Truitt,[2] to the corresponding cyclopentene by the use of phosphorus oxychloride. The olefin can be converted to a 1,2-diol which

in turn can be dehydrated to form 2-(2-pyridyl)-cyclopentanone.

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VITA

The author was born in Chicago, Illinois on June 15, 1922. He attended the public schools of that city and was graduated from Carl Schurz High School in February, 1940. In the fall of that year he entered Illinois Wesleyan University in Bloomington, Illinois. He was graduated with the degree of Bachelor of Science in December, 1943. Having enlisted in the Navy in November, 1942, he was called to active duty in March, 1944. He was discharged from the Navy in July, 1946, at which time he entered the Graduate College of the University of Illinois. In June, 1947, he received his Master of Science degree from that institution.